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14. ABSTRACT Epidemiological and animal studies associate high levels of dietary fat with increased risk of sex hormone mediated cancer, such as breast cancer. A high intake of total fat and omega-6 fatty acids increases risk while omega-3 (n3) fatty acids are associated with risk reduction. Our proposal is testing the effect of dietary fat and fatty acids on sex hormone concentrations in post-menopausal women. The objectives are to evaluate 1) the effects of total fat and n3 intake on plasma and urinary sex hormone levels, 2) the relationship between plasma fatty acids and plasma and urinary sex hormones, and 3) the effects of total fat and n3 on the association between sex hormone concentrations and urinary prostaglandin E2 (PGE2). We are performing a randomized, Latin square-designed controlled feeding study testing High Fat, Low Fat, and Low Fat + n3 diets, each of 8 week duration. In order to determine the estrogenic effects of the diets, sex hormone endpoints will be measured reflecting availability, metabolism, and action. Plasma fatty acids fractions and urinary PGE2 will be measured to evaluate mechanistic effects. At present 48 women have been screened by telephone, 16 have been screened in the clinic and 12 are currently enrolled in the trial. Eight subjects have completed all aspects of the trial. Initial data analysis is being started this summer of the sex hormone samples. No data has yet been generated.

15. SUBJECT TERMS
dietary fat, omega-3 fatty acids, eicosanoids, sex hormones

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Introduction

Our project addresses important questions about the effects of dietary total fat and fatty acids on sex hormone concentrations in postmenopausal women. The study is being conducted at the General Clinical Research Center of the University of Minnesota. Our guiding hypothesis is that dietary total fat and fatty acid content affect sex hormone concentrations in a manner associated with sex hormone mediated cancer risk. The specific objectives are 1) to evaluate the effects of total fat and omega-3 fatty acid intake on plasma and urinary sex hormone levels in postmenopausal women, 2) to evaluate the relationship between plasma concentrations of specific fatty acids and concentrations of plasma and urinary sex hormones, and 3) to evaluate the effects of total fat and omega-3 fatty acids on the association between sex hormone concentrations and urinary prostaglandin E_2 and thromboxane B_2 concentrations.

We are conducting a well controlled feeding study to evaluate the role of fat and fatty acids in 24 healthy, postmenopausal women. The diets being tested include a "high risk" American diet (40% fat), a low fat diet (20% fat) and a low fat diet with supplemental omega-3 fatty acids (23% fat). Endpoints are being measured to assess availability, metabolism, and action of sex hormones in response to the diets. Plasma fatty acids fractions and urinary prostaglandin E_2 is being measured to evaluate mechanistic effects of dietary fat.

Increased understanding of the mechanisms by which dietary fat affect sex hormone action may provide critical information for the development of cancer-preventative dietary recommendations. Nutrition information provided as focused guidelines regarding fat intake can be developed for public use that indicate which types of foods to include in the daily diet and which to avoid.

Body

Study Progress:

The project is proceeding along the time line as defined in our statement of work. We received final approval to initiate the project from the University of Minnesota Human Subject Protection Program/Internal Review Board on 10/29/2004.

Extensive recruitment efforts are ongoing. We advertise throughout the medical campus and surrounding campus buildings and through a text ad in the Fairview University Medical Center staff and patient flier. To date 48 subjects have been screened by telephone, 16subjects have been screened at the research center and 12 subjects have been enrolled in the feeding trial. Of these 12 subject, eight have completed all aspects of the study.

Personnel:

The following personnel are presently supported on this grant
Susan Raatz PhD RD, Principle Investigator (5% effort)
Mindy Kurzer PhD, Co-investigator (5% effort)
J Bruce Redmon MD, Co-investigator (5% effort)
Michael Walcher, Senior Scientist (25% effort)
Krista Lundquist, Student Food Service Worker (50% effort)

Shanna Miller, Student Food Service Worker (25% effort)
Lindsay Orr BA, Graduate Research Assistant (50% effort)

Key Research Accomplishments

Presently no data have been generated. We are presently initiating the initial analysis of the sex hormone and fatty acid data and will have data generaled by the end of the summer.

Reportable Outcomes

Training:

This project was included as a rotation project for the Minnesota Consortium for Complementary and Alternative Medicine (CAM) Clinical Research predoctoral Summer Internship from May through August 2005, Lindsay Orr, BA, a graduate student in Human Nutrition, worked on the project though this mechanism. She is the current Graduate Research Assistant working on and funded by this project. Lindsay has been performing coordination duties for this trial and will be directly involved in the sex hormone analysis in the laboratory of Mindy Kurzer, PhD.

Support from this project assisted Lindsay Orr in the attendance of the Nutrition and Cancer Prevention Practicum March 20-24, 2006 at the National Cancer Institute in Rockville, MD. NIH

Data Presentation:

"Dietary Fat, Eicosanoids and Breast Cancer Risk" was presented as a poster session on September 26, 2005 at the University of Minnesota Women's Health Research Conference (see Appendix 1).

Conclusions

The study is progressing as projected on the "Statement of Work". Given the nature of a long term feeding trial, no reportable data has yet been obtained. The study progress is as expected with recruitment of participants proceeding smoothly. The test diets are well accepted by the participants, all endpoint visits have gone well.

References

None

Appendices

Abstract from Women's Health Seminar

Appendix 1: Women's Health Seminar Poster Presentation

Dietary Fat, Eicosanoids and Breast Cancer Risk

Susan Raatz PhD RD, Mindy Kurzer PhD, J Bruce Redmon MD, Lindsay Orr BA
University of Minnesota, Departments of Medicine and Nutrition, Minneapolis, MN

BACKGROUND

- Sex hormone mediated cancers, such as breast cancer, present a significant problem in the United States.
- Safe and effective preventative strategies for these diseases are needed.
- Dietary fat is associated with risk of development of breast cancer. Specifically a high intake of omega-6 fatty acids increases risk while omega-3 fatty acids are associated with risk reduction.
- Although the association between dietary fat and sex hormone mediated cancers is unclear, it is likely due to mechanisms of endocrine balance, eicosanoid production, or immune function.

HYPOTHESIS

"Increased concentration of circulating ω3 fatty acids will reduce the biochemical markers associated with increased risk for developing certain sex hormone mediated cancers such as breast cancer"

The specific objectives are to evaluate:

- the effects of total fat and omega-3 fatty acid intake on plasma and urinary sex hormone levels in postmenopausal women,
- the relationship between plasma concentrations of fatty acids and of plasma and urinary sex hormones, and
- the effects of total fat and omega-3 fatty acids on the association between sex hormone concentrations and urinary prostaglandin E_2 and thromboxane B_2 concentrations.

MATERIALS AND METHODS

- A well-controlled feeding study
- 24 healthy postmenopausal women
- The diets to be tested in 3 8-week feeding periods include:
  - High Fat, "high risk" American diet (40% fat)
  - Low Fat (20% fat)
  - Low Fat diet with supplemental Omega-3 Fatty Acids (23% fat)
- Endpoint measures at baseline, 4, and 8 weeks of each dietary treatment:
  - *Endpoints associated with increased risk factors for breast cancer risk:* plasma estradiol (E2), estrone (E1), estrone sulfate (E1 sulfate), testosterone, androstenedione, sex hormone binding globulin (SHBG), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS).
  - *Measures of estrogen action:* plasma follicle stimulating hormone (FSH), urinary estrogen metabolites.
  - *Measures of systemic arachidonic acid-derived eicosanoids:* urinary bicyclo-prostaglandin E2 (PGE2), 2,3-dinor thromboxane B2 (TXB2).
  - *Measures reflecting influence of dietary fat and fatty acid intake:* plasma phospholipid, cholesterol ester, triglyceride and free fatty acid composition.

Dietary Intervention

Nutrient Distribution of Diets (% energy)

	CHO	PRO	FAT	PUFA	MUFA	SFA
High Fat	45	15	40	13.3	13.3	13.3
Low Fat	65	15	20	6.7	6.7	6.7
Low Fat +ω3	62	15	23	9.7	6.7	6.7
Cholesterol	100 mg/1000 kilocalories					
Dietary Fiber	10-12 gm/1000 kilocalories					

Sample Menus

PROGRESS AND RESULTS

- Recruitment began in November 2004
- 19 potential participants screened by telephone
- 6 participants currently enrolled
- First participant will complete study in December 2005
- Samples to be analyzed for first cohort of 4 participants in Jan/Feb 2006
- Recruitment efforts are continuous

RELEVANCE

Increased understanding of the mechanisms by which dietary fat affects sex hormone action may provide critical information for the development of cancer-preventative dietary recommendations. If our omega-3 fatty acid based hypothesis proves to be correct, we have the potential to reduce disease burden in the population. Nutrition information, provided as focused guidelines regarding fat intake, can be developed for public use and would indicate which types of foods to include in the daily diet and which to avoid.

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